

Changes in functional brain networks during epileptogenesis in a rodent model of temporal lobe epilepsy

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Introduction

Temporal lobe epilepsy (TLE) is the most common form of epilepsy in adults. Research has shown that abnormal functional brain networks are involved in the development of epilepsy and in the generation and spread of seizures. Gaining more insight into these networks can be useful for the development of new epilepsy therapies. Resting-state functional magnetic resonance imaging (rs-fMRI) can visualize changes in neural activity on a whole-brain level and can be used to identify functionally connected brain regions and functional networks. In this study, we aim to map changes in functional networks during epileptogenesis in the systemic kainic acid rat model of temporal lobe epilepsy using resting-state fMRI and graph theory.

Methods

Three adult male Sprague-Dawley rats (426 ± 23 g body weight) were included in a pilot study. The animals were intraperitoneally injected with kainic acid (KA) according to the protocol of Hellier et al. (1998) resulting in status epilepticus (SE). Rs-fMRI images were acquired before the KA injections and at 5 time points during the development of epilepsy: 1, 3, 9, 12 and 17 weeks after the KA injections. At each time point an anatomical TurboRARE T2 image and two resting-state blood-oxygen level dependent (BOLD) fMRI images (TR=2s, TE=20ms, 300 repetitions) were acquired on a 7T system (Bruker PharmaScan). During image acquisition the animals were anesthetized with medetomidine. The fMRI images were corrected for slice timing and motion, normalized to a template, smoothed with a Gaussian kernel (FWHM=0.8 mm), and band-pass filtered (0.01-0.1 Hz) using SPM12. The mean time series of 40 predefined regions of interest (ROIs) were extracted from the preprocessed images and the Pearson correlation coefficient between each pair of ROIs was calculated and stored in a correlation matrix using a graph theoretical network analysis toolbox (GRETNA). Different thresholds were applied to the correlation matrix to remove the weakest connections, resulting in 21 correlation matrices with a density ranging from 20% to 40%. Each of these matrices was visualized as a graph in which the nodes represent the ROIs and the edges the correlation coefficients between the time series of the ROIs. Five network measures were calculated: the correlation coefficient and the local efficiency (measures of segregation), the characteristic path length and the global efficiency (measures of integration), and the small-world coefficient. The network measures were calculated for each correlation matrix and the z-scores of the measures were plotted as a function of network density. The mean value was calculated over this range of densities and plotted as a function of time to visualize how the properties of the functional networks change during the development of epilepsy.

Results

Visualization of the network measures as a function of time shows that during the first three weeks after the KA injections, the clustering coefficient and the local efficiency increase, indicating an increased segregation of the functional network. The characteristic path length increases and the global efficiency decreases, indicating a decreased integration, and the small-world coefficient increases, indicating an increase in small-worldness. After these first weeks, there is a decrease in segregation and small-worldness and an increase in integration, and 17 weeks after the KA injections, when the latency period is over, the network measures have returned to their baseline values.

Conclusion

The results of this pilot study suggest that there is an increased segregation, a decreased integration and an increased small-worldness in the functional brain network during the first three weeks after KA injections in the KA rat model for TLE. After three weeks, the network measures start to return to their baseline values.

References

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